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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/636,243
Filing Date: August 10, 2000
Appellant(s): WANG ET AL.

Dahna Pasternak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/28/09 appealing from the Office action mailed 5/1/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

This appeal involves claims 5-6 and 20-21.

Claims 1-4 and 7-19 have been canceled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Pomerantz et al, Structure-based design of a dimeric zinc finger protein, Biochemistry, vol. 37, No. 4, Jan. 1998, pages 965-970.

Krylov et al, A thermodynamic scale for leucine zipper stability and dimerization specificity: e and g interhelical interactions, EMBO J., vol. 13, No. 12, 1994, pages 2849-2861.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

Claims 5-6 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pomerantz in view of Krylov.

The Board in their decision made on 5/30/07 gave a new ground of rejection below:

The Pomerantz publication has been described for its disclosure of a zinc finger fused to the naturally occurring

dimerization domain extracted from the GAL4 protein. Pomerantz's fusion protein differs from the fusion protein contained in the zinc finger complex of claim 5 by having a naturally occurring dimerization domain, instead Pomerantz points the skilled artisan directly to prior art publications that teach modified dimerization domains. Such domains are nonnaturally occurring and "join each other by specific binding," meeting the requirements of the claimed "peptide linkers." See claim 5. In particular, reference 19 (hereinafter"Krylov"), cited by Pomerantz for its studies of the coiled-coil interaction motif, describes "protein design rules that can be used to modify leucine zipper-containing proteins to possess novel dimerization properties." Krylov, page 2850, column I. "33 different leucine zipper proteins containing 27 different systematic combinations of amino acids" were produced. Id., page 2856, column 2 ("Discussion"). See also Fig. IB for a list of exemplary "mutant proteins." Id., page 2850, column 2. The mutant proteins were mixed together under conditions which facilitated dimer formation. By measuring the stability of the dimers formed (id., page 2852-53, "Thermodynamic stability"), Krylov was able to demonstrate that certain modified dimers had increased stability• and specificity as compared to the unmodified form. "Novel heterologous interactions regulate dimerization

specificity .... In the second mixing experiment, the stability of the heterodimer is calculated to be greater than the average of the two homodimer stabilities, thus favoring the formation of heterodimers." Id., page 2856, columns 1-2.) Thus, the element missing from Pomerantz - non-naturally occurring peptide linkers - is supplied by Krylov. The skilled worker would have had a reasonable expectation that Krylov's domains could be utilized to complex zinc fingers to which they are attached in view of Krylov's success in not only modifying their binding activity, but in making it stronger (i.e., more stable). Krylov also teaches dimerization domains having the same sequence, meeting the limitations of clam 6. See e.g., id., page 2856, column I, describing homo- and heterodimers, where the homodimers have "the same sequence." Pomerantz describes dimers between ZFGDI fusion protein, where each fusion contains the same zinc finger. Pomerantz, Abstract ("a dimeric zinc finger protein, ZFGDI"). This meets the requirements of claim 20. In sum, we find that Pomerantz and Krylov disclose all elements of the subject matter recited in claims 5, 6, and 20. For the reasons discussed above, the skilled worker would have considered these claims obvious in view of Pomerantz's express suggestion to combine its teaching with Krylov (i.e., reference 19), and Krylov's disclosure that

would have led the skilled worker to reasonably expect that the combination would work.

(10) Response to Arguments

Appellants argue that the Gal4 dimerization domain used in Pomerantz is fully 50 amino acids in length (see, Figure 1 of Pomerantz). Notably, this does not include a 9 amino acid peptide linker used to join the zinc fingers to the dimerization domain. Thus, Pomerantz, at best, discloses modifying an almost 60 amino acid dimerization domain and linker, which is twice as long as in the claimed complexes. Simply put, Pomerantz does not teach or suggest non-naturally occurring peptide linkers of the claimed lengths.

In reply, Figure 1, page 968 of Pomerantz shows at the bottom panel that the dimerization domain is from 41 to 65 residues (i.e., 24 amino acid residues) in length starting from the Cα of serine 41 from GAL4 (the first residue in the linker.)

Figure 1 is fully described by Pomerantz at e.g., page 967, col. 1, under the heading RESULTS. Pomerantz teaches that the chimeric protein is predicted to bind to a 25 base-pair site with the sequence 5'-CGCCCAGAGGACAGTCCTCTGGGCG-3'. The 6 base-pair zinc finger subsites (underlined) are present on each end of the extended site. The central 13 base pairs are **derived from**

a portion of the GAL4-binding site that lies under the **coiled-coil dimerization motif** and associated polypeptide linker.

Pomerantz clearly teaches throughout the article that it is the motif (short linker) of GAL4 that is used to fuse the two proteins as follows:

1. Page 965, abstract, Pomerantz teaches that computer modeling was used to design a dimeric zinc finger protein with a **portion** of the dimerization domain of GAL4.

2. Paragraph bridging pages 965 and 966, Pomerantz teaches that in the computer modeling for fusing two heterologuous modules **short linkers** are used.

3. Page 966, second complete paragraph, Pomerantz discloses that the GAL4 domain (i.e., 41-100 in Fig. 1) contains a **coiled-coil motif**, a simple, well-understood structure that can further be modified for design purposes. The GAL4 dimerization **motif** is interesting because it docks to DNA and presumably would help to position and orient the fused zinc finger domains.

4. Page 967, col. 2, Pomerantz teaches the **central 13 base pair region** (see above) is replaced by a sequence unrelated to the natural Gal4-binding site.

5. Page 968, under the heading DISCUSSION, Pomerantz discloses the simple coiled-coil based dimerization **motif** that allows for homo-or heterodimerization.

6. Page 969, Figure 2, Pomerantz teaches the central 13 bp **derived** from the GAL4 binding site (white bar).

The coiled-coil region is known to be useful as a linker for numerous fusion protein as evident from the numerous prior art cited by Pomerantz(e.g., Krylov, Marmorstein) and appellants in the instant disclosure.

The specification at e.g., page 36, lines 2-12 recites:

> **..Zhang et al. (19) have isolated dimerization elements by fusing 5 random fragments** of the yeast genome to the DNA-binding domain of lambda repressor and selecting fusion proteins that reconstitute repressor activity. This group reached similar conclusions regarding the frequency of **functional dimerization domains.** [See also references (20-22) cited therein.] (Emphasis supplied).
>
> Even assuming that Pomerantz teaches a 60-residue linker, as argued, however, Pomerantz employed this only to show the full sequence of the Gal4 dimerization domain. Pomerantz teaches at e.g., page 967 col. 1, that structural information is not available for residues 66-100 which forms a part of the GAL4 dimerization domain. (It is also not apparent how the claim 30-residue linker without any description of its structure can link/fuse any zinc finger complexes.)

Appellants argue that Krylov's dimerization domain is altered in its natural context of the leucine zipper protein as a whole. (Krylov, left column of page 2850 to left column of page 2851 and Fig. 1):

The protein sequence of the first four leucine zipper heptads of the host or parent protein, the bZIP protein VBP (Iyer et al., 1991) is presented in Figure 1B ..... The lower section of Figure 1B presents the nomenclature used to describe our various mutant proteins.

Appellants further argue that there is nothing in Krylov (or Pomerantz) that teaches this domain could be isolated from its natural context and used to dimerize zinc finger proteins. (See appellants' arguments below as to Krylov's 32 amino acids being isolated.)

In reply, attention is drawn to Pomerantz at e.g., Figure 2, discussed above, which shows the isolated (i.e., derived) motif of GAL4 linking the two proteins.

Appellants further argue that Krylov's dimerization domains are at least 37 amino acids in length (4 heptads and 3 N-terminus amino acids and 2 C-terminal amino acids). See, Figure 1B of Krylov. **Even if only the heptads (32 amino acids) were isolated from Krylov**, Pomerantz teaches that a separate linker would be needed to join the dimerization domain to the zinc

fingers. See, Figure 1 of Pomerantz. Accordingly, once linked to the zinc fingers, even the shortest possible heptad repeat of Krylov would still be over 40 amino acids. (Emphasis added.)

In response, Krylov at e.g., page 2850, Fig. 1B teaches a coiled coil heptads, which is 24 amino acids long commencing from letter d (leucine) of the coiled-coil repeating heptad sequence (at most 29 of the coiled-coil interacting domain). Krylov states:

> (B) The amino acid sequence of the **leucine zipper region** of VBP is presented using the single-letter code. Below the VBP sequence is the nomenclature for the positions in a coiled coil. The sequence starts at the first 'leucine' position as defined previously (Vinson et a 1989) and is grouped into heptads (g,a,b,©,d,e,f)….

Appellants finally also reiterate that the claims require that the peptide linker be non-naturally occurring. As clearly defined in the as-filed specification, a non-naturally occurring peptide linker is one that lacks significant sequence identity with a naturally occurring peptide (see, e.g., page 3, lines 22-24 of the as-filed specification):

> The invention provides non-naturally occurring dimerizing peptides. Some such peptides are homo-dimerizing peptides. Such peptide typically lack significant sequence identity with a naturally occurring peptide.

In reply, both the dimers of Pomerantz and Krylov are derived peptides. Each is a short length peptide which therefore lacks significant sequence identity with a naturally occurring peptide, as read in the light of the above-cited definition in the specification. The art also defines non-naturally occurring as a recombinantly/synthetically made peptide or mutants as the ones created or taught by Krylov. These mutants are therefore non-naturally occurring as these lack significant sequence identity with the natural leucine zipper peptide, consistent with the definition in the specification.

Appellants argue that the obviousness rejection is improper because the proposed combination of using Krylov's altered leucine zipper dimerization domains, shortening these domains to less than 30 amino acids and using these truncated domains in place of Pomerantz's GAL4 dimerization domains is not predictable from the teachings of the references and/or state of the art.

In reply, Pomerantz reliance on Krylov is not based on substituting the coiled-coil linker Leu zipper of Kyrlov to the GAL-4 of Pomerantz. Rather, Pomerantz discloses that the coiled-coil region (a simple, well-understood structure) of GAL4 can similarly be modified by mutation of

the residues as taught by Krylov for the known, common coiled-coil structure as leu-zip. Each of the Pomerantz and Krylov references already teaches dimerization domains that are less than the claim undefined 30-residue length peptide. See rejections above.

There is nothing new, unobvious or unpredictable in varying the length of a known dimerization linker when its sequence is known and is varied in the context it is used. The prior art and the specification (page 15, line 16) recognize the requirement for this linker to be of short length to be functional.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/TERESA WESSENDORF/

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